

REMARKS

Upon entry of the foregoing amendment, claims 2-12, 18-22, 25, 26 and 28-38, 42, 43, and 47-52 are pending in the application, with claims 1, 13-17, 23-24, 27, 39-41 and 44-46 canceled without disclaimer of, or prejudice to, the matter as originally claimed. Although claims 1-27 have been withdrawn by the Examiner under 35 U.S.C. § 121, Applicant has amended method claims 2-12, 18-22, 25 and 26 to include the limitations of the product claims such that upon allowance of the product claims, the method claims may be rejoined. Currently, claims 28-38, 42-43, and 45-52 stand rejected as not enabled under 35 U.S.C. § 112, first paragraph, and as obvious under 35 U.S.C. § 103(a).

Independent claims 2, 4, 28, 30 and 42 are amended to clarify that the compositions and methods of the present invention are able to increase at least one of the DR4 or DR5 death receptors in at least a portion of the treated prostate cancer cells. Support for the amendment of the claims is found in the specification at pages 19-20, and 30-31 (Example 5), and Figure 2, where it is shown that application of TRAIL and Mifepristone upregulated the expression of DR5 in LNCaP cells (androgen responsive) and LNCaP C4-2 cells (androgen-insensitive), and where DR4 was increased in LNCaP cells, but not significantly in LNCaP C4-2. Other amendments are made to improve the syntax and to use consistent wording in the claims (e.g., claims 18 and 20-22 are amended to be consistent with claims 47-51) and are supported by the claims as originally filed. Accordingly, no new matter is added by the amendments to the claims.

The Rejection of the Claims Under 35 U.S.C. 112, First Paragraph is Traversed or Rendered Moot

The Examiner stated that

[T]he specification, while being enabling for a composition comprising an effective amount of the TRAIL polypeptide comprising SEQ ID NO: 1 and an antiprogestin, which effective amount increases the death receptor DR4 or DR5 in a portion of the treated prostate cancer cells, does not reasonably provide enablement for a composition comprising an effective amount of a TRAIL polypeptide comprising SEQ ID NO: 1 and an antiprogestin, wherein an effective amount of TRAIL polypeptide SEQ ID NO: 1 and an antiprogestin results in an increase in

‘at least one death receptor’ or ‘at least’ one of DR4 or DR5, in a portion of the treated prostate cancer cells.

Office Action at page 2.

Applicant has amended the claims to recite that the compositions and methods of the present invention are able to increase the levels of at least one of the DR4 or DR5 death receptors in at least a portion of the treated prostate cancer cells. Applicant respectfully asserts that the wording “at least one of DR4 or DR5” (i.e., DR4 and/or DR5 as opposed to DR4 or DR5) is supported by the specification at pages 19-20, and 30-31 (Example 5), and Figure 2, where it is shown that application of TRAIL and Mifepristone upregulated the expression of DR5 in LNCaP cells (androgen responsive) and LNCaP C4-2 cells (androgen-insensitive), and where DR4 was increased in LNCaP cells, but not significantly in LNCaP C4-2. Thus, certain types of prostate cancer cells (e.g., LNCaP) may have an increase in DR5 and DR4, where other types of prostate cancer cells (e.g., LNCaP C4-2) may have an increase in DR5 or DR4.

For at least these reasons, the Applicant requests that the rejection of the claims as not enabled under 35 U.S.C. § 112, first paragraph, be withdrawn.

The Rejection of the Claims Under 35 U.S.C. 103 is Traversed or Rendered Moot

A. Prima Facie Obviousness

1. Claims 28-38, 45-52

The Examiner rejected claims 28-38 and 45-52 under 35 U.S.C. 103(a) as being allegedly unpatentable over Bonavida, B. et al., 1999, Int. J. Oncology 15(4):793-802 (hereinafter “Bonavida”), in view of Wiley et al., WO 97/01633-A1 (hereinafter “Wiley”), Fathy El Etreby et al., 2000, The Prostate 42: 99-106 (hereinafter “El Etreby 2000”), and El Etreby et al., 1998, Breast Cancer Res. Treat., 51: 149-168 (hereinafter “El Etreby 1998”).

Applicant has amended the claims to describe a composition for treating prostate cancer by inducing cell death in androgen responsive and androgen independent prostate cancer cells, where the composition comprises an effective amount of a TRAIL polypeptide comprising the amino acid sequence SEQ ID NO: 1 and an antiprogestin of

Mifepristone in a pharmaceutical carrier, wherein an effective amount comprises sufficient TRAIL polypeptide and antiprogesterone or Mifepristone to induce apoptosis in at least a portion of the androgen responsive and androgen independent prostate cancer cells and to increase the level of at least one of the DR4 or the DR5 death receptors in at least a portion of the prostate cancer cells exposed to the composition, such that the combination of the TRAIL and the antiprogesterone induces apoptosis in a greater number of the treated prostate cancer cells than the additive effect of TRAIL and the antiprogesterone separately applied to the cancer cells. Applicant respectfully asserts that there is no suggestion by the references, either alone or in combination, that combining TRAIL with an antiprogesterone would be effective in prostate cancer cells, such as androgen responsive LNCaP cells that are refractory to treatment by either TRAIL or an antiprogesterone, or that the combination of TRAIL and Mifepristone would be more effective than the additive effect of the TRAIL and the antiprogesterone separately applied to the cancer cells.

Applicant respectfully asserts that the Examiner has not established a *prima facie* case of obviousness. The Federal Circuit has stated that “[i]n order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method.” *Motorola, Inc. v. Interdigital Technology Corp.*, 43 U.S.P.Q. 2d 1481, 1489 (Fed. Cir. 1997) (quoting *Beckman Instruments, Inc. v. LKB Produkter AB*, 13 U.S.P.Q. 2d 1301, 1304 (Fed. Cir. 1989)). Also, subsection 706.02(j) of the MPEP states that to establish a *prima facie* case of obviousness three criteria must be met:

- (i) a suggestion or motivation to modify or combine references;
- (ii) a reasonable expectation of success; and
- (iii) all the limitations in the claim(s) must be taught or suggested by the reference, or combination of references.

The Applicant respectfully asserts that none of the criteria for a determination of obviousness have been met. Thus, the Applicant respectfully asserts that the combination of the cited references do not provide a motivation or suggestion to combine the references with a reasonable expectation of success, such that all the limitations in the claims are taught or suggested.

Bonavida and Wiley

The Examiner cites Bonavida as teaching two strategies that can be used to sensitize resistant cancer cells to TRAIL-mediated apoptosis: (1) the suppression of an anti-apoptotic molecule (e.g., Bcl-XL or Bcl-2, death inhibitors or anti-apoptotic proteins); or (2) the up-regulation of a pro-apoptotic molecule. The Examiner stated that Bonavida describes the inhibition of Bcl-XL by actinomycin. The Examiner further stated that Bonavida describes that TRAIL apoptosis involves cross[link]ing of TRAIL receptors DR4, DR5 with the ligand TRAIL. The Examiner cited Wiley as providing the sequence of SEQ ID NO: 1 for TRAIL. Office Action at pages 8-9.

Bonavida describes TRAIL in combination with cyclohexamide (an inhibitor of protein translation) in melanoma, TRAIL in combination with adriamycin (an antibiotic) in multiple myeloma, or TRAIL in combination with actinomycin D (a non-specific terminator of mRNA transcription) in certain prostate cancer cell lines. Although Bonavida notes that actinomycin D may be used to inhibit the synthesis of Bcl-XL, there is no description in Bonavida that the broad-based, non-specific inhibition of transcription of all mRNAs being synthesized in the cell (and not just Bcl-XL) by actinomycin-D is in fact overcoming resistance to TRAIL via an inhibition of Bcl-XL. Nor, is there any description in Bonavida that application of actinomycin D may be used to inhibit Bcl-2, or other anti-apoptotic proteins.

Also, with respect to prostate cancer, Bonavida shows, in contrast to Applicant's invention, that there is no correlation between expression of prostate cancer cell death receptors (DR4, DR5, DcR1 and DcR2) and the sensitivity of the cells to killing by TRAIL and actinomycin D, indicative that the action of actinomycin D is NOT via pathways that involve DR4 and/or DR5 (see Bonavida at page 799, column 1 and Table IV). Thus, although Bonavida describes the general understanding that TRAIL acts by inducing cross-linking of DR5 and DR4, one reading Bonavida would not be motivated to use TRAIL for treatment of prostate cancer as the effect for TRAIL and actinomycin D does not appear to be specific to the death receptors known to mediate the effects of TRAIL but appears to work by a more generalized and non-specific mechanism. Also, reading Bonavida, there would be a very low expectation of success of using another

agent in combination with TRAIL to provide a composition or method treat prostate cancer by increasing apoptosis in a specific, death receptor-mediated manner.

Thus, Applicant respectfully asserts that Bonavida suggests only that certain relatively nonspecific agents may be combined with TRAIL to increase cell killing, as Bonavida describes using TRAIL with chemotherapeutics that work by different (and more generalized) biochemical pathways (e.g., actinomycin D, adriamycin, and cyclohexamide) than antiprogestins. Bonavida does not, however, suggest that these general chemotherapeutic agents would act in a manner similar to an antiprogestin to induce cell death in prostate cancer. Also, Applicant respectfully notes that other references (e.g., Gliniak previously cited by the Examiner), in contrast to Bonavida, teach that many chemotherapeutic agents, including cisplatin, 5-fluorouracil, mitomycin, etoposide, or Adriamycin (in contrast to Bonavida above), all of which would be expected to have the ability to reduce apoptosis by inhibiting synthesis of apoptotic cellular machinery (e.g., enzymes, receptors, and the like), did not result in an enhancement of cytotoxic activity by TRAIL.

El-Etreby 2000 and El-Etreby 1998

The Examiner noted that Bonavida does not teach or suggest the combination of an antiprogestin and TRAIL for treatment of prostate cancer. Thus, the Examiner stated that:

Bonavida, B et al do not teach an antiprogestin or Mifepristone in combination with TRAIL. Bonavida, B et al do not teach: 1) packaging of Mifepristone and TRAIL, such that Mifepristone is at least partially released prior to the release of said TRAIL, or are released substantially simultaneously, 2) the dose of TRAIL, which ranges from 1 to 1,000 ng/ml, 200-600 ng/ml, 350-450 ng/ml, and 3) the does of Mifepristone, which rages from 1 to 1,000 μ M, 1 to 100 μ M or 5 to 20 μ M.

El Etreby et al, 2000, teach Mifepristone, an antiprogestin, which is a known inhibitor of mammary tumor, also significantly inhibit both androgen-sensitive (LNCaP) and androgen-insensitive (LNCaP C4-2) human prostate cancer cells, grown in nude mice (see Results on pages 102-103). Fathy El Etreby et al teach that the antitumor action of antiprogestins is mediated via the progesterone receptor, and related to induction of apoptosis (p. 100, first column, first paragraph).

El Etreby et al., 1998, teach that treatment with Mifepristone or 4-hydroxy-tamoxifen induces 60% inhibition of Bcl2, a negative regulator of apoptosis, in a breast cancer cell line.

Office Action at page 9. El Etreby 2000 describes that Mifepristone can exhibit anti-tumor activity in androgen-sensitive and androgen-insensitive prostate cancer cells and suggests that Mifepristone may be associated with apoptosis. However, the experiments in El Etreby 2000 do not measure apoptosis or other cellular markers, but only show the effects of Mifepristone on tumor growth and tumor volume. Also, El Etreby 2000 does not describe or suggest the use of TRAIL for inhibition of prostate cancer. Also, El Etreby 2000 is primarily concerned with the development of agents for the treatment of androgen-insensitive prostate cancer cells, and does not describe, teach, or suggest that Mifepristone, or other antiprogestins, may be used to increase the sensitivity of TRAIL-resistant, androgen-sensitive prostate cancer cells, such as LNCaP cells, or that compositions having this ability may be clinically important. Nor, does El Etreby 2000, in combination with Bonavida or El Etreby 1998 (discussed below), describe, teach or suggest that antiprogestins, such as Mifepristone, may act in a synergistic manner with TRAIL, at the level of the TRAIL pathway.

El Etreby 1998 describes that Mifepristone (either alone or in combination with tamoxifen) can inhibit breast cancer growth and the synthesis of bcl-2. Applicant respectfully asserts that this finding, alone or in combination with Bonavida and El Etreby 2000 does not describe, teach or suggest Applicant's claimed invention. First, although bcl-2 is known to be expressed in androgen-insensitive prostate cancer cells (e.g., LNCaP C4-2), it is not detected in significant amounts in androgen-sensitive cells, such as the TRAIL-resistant LNCaP cells described by the Applicant (see e.g., Chaudhary et al., Environ. Health Perspectives, 1999, 107(Suppl-1):49-57 at page 53, col. 2; submitted herewith as a Supplemental IDS). In contrast, Applicant has shown that it is the androgen-sensitive prostate cancer cells that are refractory to treatment with TRAIL. Thus, one reading El-Etreby 1998 would not be motivated to use Mifepristone to increase bcl-2 in prostate cancer as a means to overcome resistance to TRAIL via inhibition of bcl-2 or other members of the apoptotic pathway, as there was no evidence that the activity of bcl-2 is significant in the type of prostate cancer cells that are resistant

to TRAIL (i.e., androgen-sensitive LNCaP cells). Also, there would be no expectation of success that Mifepristone could be used to render TRAIL-resistant androgen-sensitive cells sensitive to treatment by TRAIL as there is no teaching, description, or suggestion that Mifepristone or other antiprogestins would be effective in reducing the resistance of androgen sensitive cells (LNCaP) to TRAIL since the resistance of such cells to TRAIL does not appear to be associated with an increase of bcl₂ or other members of the apoptotic pathway, but would be expected to be the result of another effector.

Thus, the combination of the references, Bonavida, El Etreby 2000 and El Etreby 1998, in view of the sequence provided by Wiley, to not describe, teach or suggest the limitations of a composition (or method) for treating prostate cancer by inducing cell death in androgen responsive and androgen independent prostate cancer cells comprising an effective amount of a Tumor necrosis factor α - Related Apoptosis Inducing Ligand (TRAIL) polypeptide comprising the amino acid sequence SEQ ID NO: 1 and an antiprogestin in a pharmaceutical carrier, wherein an effective amount comprises sufficient TRAIL polypeptide and antiprogestin to induce apoptosis and to increase at least one of the DR4 or the DR5 death receptors in at least a portion of the treated prostate cancer cells exposed to the composition such that the combination of the TRAIL and the antiprogestin induces apoptosis in a greater number of the treated androgen responsive and androgen independent prostate cancer cells than the additive effect of TRAIL and the antiprogestin separately applied to the cancer cells

Applicant again asserts that the fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. See e.g., *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994); MPEP 4144.08. The nature of the various agents used in combination with TRAIL as described by Bonavida (e.g., actinomycin D, a general transcription terminator; Adriamycin, an antibiotic; cyclohexamide, a general inhibitor of protein translation) describe a very large genus of chemotherapeutic agents. Even if such compounds can, in certain cases, act as inducers of apoptosis or inhibitors of anti-apoptosis, as for example by the non-specific inhibition of transcription of the Bcl-XL protein, there is little suggestion that such agents can be used interchangeably with an antiprogestin such as Mifepristone. El Etreby 2000 only adds that antiprogestins are specific to certain progesterone-receptor mediated

cancers, providing an additional basis for distinguishing antiprogestins from the chemotherapeutic agents used by Bonavida. El Etreby 1998 actually teaches away from Applicant's invention in that it would not be expected that Mifepristone would be able to induce apoptosis by inhibition of bcl-2 in androgen-sensitive cells, since such cells do not express high amounts of this anti-apoptotic protein. Thus, one would not be motivated to substitute an antiprogestin (as used by El Etreby to inhibit production of bcl-2) for the non-specific agent actinomycin D (as used by Bonavida) to render androgen-sensitive (and/or androgen-insensitive cells) resistant to TRAIL.

An invention may not be deemed obvious where the prior art only provides an invitation to explore, and does not teach or suggest the Applicant's claimed invention. *In Ex parte Obukowicz*, 27 USPQ 2d 1063 (1992). Thus, the courts have held that an obviousness rejection may not be predicated on the view that the invention was "obvious to try," as for example, where the art gives only general guidance as to the particular form of the invention or how to achieve it. *In re Lindell*, 385 F.2d 453 (CCPA 1967), and *Ex parte Levensgood*, 28 USPQ 1300 (Bd. Pat. App. & Inter, 1993). Although both TRAIL and Mifepristone had been used individually with some efficacy in treating prostate cancer, there was no indication, based on the results in the cited art, that the combination of TRAIL and Mifepristone would increase TRAIL-mediated apoptosis in androgen-resistant and androgen-sensitive prostate cancer cells at a level that is greater than additive for the effects of each agent alone. Also, in contrast to Bonavida, Applicant describes compositions that act to sensitize cells to TRAIL by specifically activating the DR4/DR5 death receptor pathway, such that the effects seen with the compositions of the invention (i.e., including TRAIL and an antiprogestin) is greater than that of either agent alone.

The Examiner has stated that the combined art does not teach that: (1) a combination of TRAIL and anti-progestin or Mifepristone induces apoptosis in a greater number of the treated prostate cancer cells than the additive effect of TRAIL and the anti-progestin separately; (2) TRAIL and an antiprogestin increase either DR5 or DR4; (3) TRAIL and an antiprogestin increase an activated caspase, which is at least one of caspase-8, caspase-7, caspase-9, or caspase-3; (4) TRAIL and an antiprogestin increase truncated BID; and (5) TRAIL and an antiprogestin reduce mitochondrial cytochrome C

or increase apoptosome formation. The Examiner stated, however, that the composition comprising TRAIL and Mifepristone appears to be the same as the prior art suggested composition absent a showing of unobvious differences. Office Action at page 11.

Applicant respectfully asserts the synergy displayed by TRAIL and an antiprogestin to induce apoptosis in a greater number of the treated prostate cancer cells than the additive effect of TRAIL and the anti-progestin separately is not obvious in that there is absolutely no suggestion in the prior art that an antiprogestin would increase the effect of TRAIL in both androgen-sensitive and androgen-insensitive cells in a synergistic manner. Nor is there any description, teaching or suggestion in the combination of references that an antiprogestin would act at the level of the DR5 or DR4 death receptor, or activated caspase enzymes, to provide a specific induction of apoptosis, particularly in LNCaP cells that are not expected to have significant levels of apoptotic inhibiting agents such as bcl-2.

Thus, Applicant's specification teaches that not all prostate cancer cells are sensitive to TRAIL (see Figure 1 of Applicant's specification). For example, as taught by Applicant's specification, TRAIL does not result in a significant increase in apoptosis and/or DR5 expression in certain LNCaP androgen sensitive prostate cells. Also, such cells are not sensitive to Mifepristone at the levels used by Applicant (see the specification, FIG. 1A, 1C). As described in Applicant's specification, both TRAIL and Mifepristone can act via death domain receptors DR4 and DR5 to stimulate of caspase 8, which subsequently activates procaspases 3, 7, and 9. Applicant is therefore able to use Mifepristone to sensitize cells to TRAIL by activating the DR4/DR5 pathway. In this way, Applicant's methods maintain specificity for the TRAIL pathway for induction of cell death by an apoptosis-specific pathway. This is in contrast to the agents proposed by Bonavida which act by non-specific and non-receptor-mediated mechanisms that are much more generalized to induce cell death and thus, can result in non-specific side effects. The challenge in prostate cancer is to develop agents that specifically target both androgen-insensitive prostate cancer cells and androgen-sensitive prostate cells. Applicant respectfully asserts that the studies of El Etreby 1998 and 2000 in combination with Bonavida do not describe, teach or suggest how an antiprogestin and TRAIL may be used to treat prostate cancer cells that are refractory to TRAIL.

For at least these reasons, Applicant respectfully asserts claims 28-38 and 45-52 are not obvious over Bonavida, Wiley, El Etreby 2000, and El Etreby 1998. Thus, Applicant respectfully requests that the rejection of claims 28-38 and 45-52 as obvious under 35 U.S.C. 103(a) be withdrawn.

2. Claims 42-43

The Examiner rejected claims 42-43 under 35 U.S.C. 103(a) as being allegedly unpatentable over Bonavida in view of Wiley, El Etreby 2000, El Etreby 1998, and further in view of Presta et al., 2002/0146416, priority date March 18, 1994 (hereinafter "Presta"). The Examiner stated that Bonavida, Wiley, El Etreby 2000, and El Etreby 1998, do not teach a kit as recited in claims 42-43, but that Presta teaches mixing therapeutic formulations with physiologically acceptable carriers for storage. Office Action at pages 12-13.

Applicant respectfully asserts that claims 42-43 are not obvious over Bonavida, Wiley, El Etreby 2000, and El Etreby 1998 for the reasons stated above, and that Presta does not overcome the deficiencies of these references. Thus, Applicant respectfully requests that the rejection of claim 42-43 as obvious under 35 U.S.C. 103(a) be withdrawn.

For the reasons stated above, Applicant respectfully asserts that the Examiner has not established a *prima facie* case of obviousness for the rejection of claims 28-38, 42, 43, and 45-52 under 35 U.S.C. § 103 (a), and respectfully requests that the rejection be withdrawn.

B. Secondary Considerations

Without in any way acquiescing that the Examiner has established a *prima facie* case of obviousness, Applicant respectfully asserts that secondary considerations further substantiate that Applicant's claimed composition is not obvious in view of the cited references. Applicant has previously submitted a declaration under 37 C.F.R. § 1.132 describing why secondary considerations render the composition patentable under 35 U.S.C. § 103(a).

i. Surprising Results

First, the non-obviousness of Applicant's invention is substantiated in view of the surprising results found by Applicant that: (1) that TRAIL and Mifepristone may be used

to induce apoptosis in both androgen responsive and androgen independent prostate cancer cells; (2) combining TRAIL and an antiprogesterone such as Mifepristone is synergistic; and (3) that antiprogesterones specifically act on the TRAIL pathway and DR5 and/or DR4 death receptors.

The Examiner stated that:

The combined art does not explicitly teach that: 1) a combination of TRAIL and anti-progesterone or Mifepristone induces apoptosis in a greater number of the treated prostate cancer cells than the additive effect of TRAIL and the anti-progesterone separately, 2) TRAIL and antiprogesterone increase death receptor, which is DR4 or DR5, (3) TRAIL and antiprogesterone increase an activated caspase, which is at least one of caspase-8, caspase-7, caspase-9, or caspase-3, (4) TRAIL and antiprogesterone increase truncated BID, 5) TRAIL and antiprogesterone reduce mitochondrial cytochrome C or increase apoptosome formation, however, the claimed composition appears to be the same as the composition taught by the combined prior art, absent a showing of unobvious differences. . . . See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex Parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Office Action at page 10.

Applicant respectfully asserts that the cases cited by the Examiner deal with a very different situation than the instant invention. *Ex Parte Gray* addressed the situation where the Board of Patent Appeals and Interferences found that purified recombinant nerve growth factor (NGF) was not, as a product by process, patentably distinct from naturally occurring NGF. *In re Best* addresses whether a particular zeolite compound is patentably distinct from the same zeolite compound made by a variation of the method in which the cooling step was not specifically described but would have inherently occurred in substantially the same manner.

Unlike the cases cited by the Examiner, Applicant's composition is not substantially similar to an actual composition of the prior art. Thus, as described above, Applicant was the first to combine Mifepristone and TRAIL in such a manner such that Mifepristone sensitizes prostate cancer cells to the effects of TRAIL. Bonavida describes that actinomycin D can, by inhibition of mRNA synthesis, interact with TRAIL to overcome resistance of the cells to the effects of TRAIL. Still, for the reasons discussed above, Applicant asserts that there was no suggestion in the art that Mifepristone would

act in a similar manner as Adriamycin D, cyclohexamide, or actinomycin D. Also, as high levels of anti-apoptotic factors are not expected to be associated with androgen-sensitive (TRAIL-resistant) prostate cancer cells, it would not be expected that Mifepristone could overcome the lack of effectiveness of TRAIL in these cells by decreasing bcl-2 and other anti-apoptotic effectors.

As noted above, the challenge in prostate cancer is to develop agents that are effective in treating both androgen-sensitive prostate cells and androgen-insensitive prostate cancer cells. Thus, prostate cancer is unique in that the response of these two different cell types to certain chemotherapeutic agents can limit treatment of the cancer. Applicant was the first to discover that Mifepristone can increase the efficacy of TRAIL in inducing apoptosis in androgen-sensitive prostate cancer cells that are resistant to the apoptotic effects of TRAIL. Thus, as shown in Figure 1 of Applicant's specification, treatment of LNCaP cells with 400 ng/ml TRAIL does not alter cell survival significantly. Also, such cells were not sensitive to Mifepristone (see e.g., Figure 1A and 1C). However, treatment of LNCaP cells with Mifepristone followed by TRAIL results in a significant decrease in cell survival (Figure 1A and 1C).

Also, as shown by Applicant's specification, the combination of Mifepristone and TRAIL results in effects that are more than additive, but that display synergy. Thus, as shown in Figure 1A, for LNCaP cells at 16 h, the combination of Mifepristone plus TRAIL results in a substantially greater reduction in survival than the individual reduction for TRAIL plus Mifepristone. Similar results are seen for the measurement of apoptosis using the Apoptosense assay (Figure 1C) that measures cytokeratin exposed as a result of apoptosis.

Applicant respectfully asserts that there is nothing in the cited references that teaches or suggests the surprising synergy exhibited by the combination of TRAIL and Mifepristone, or that the combination of TRAIL and Mifepristone would be effective to treat prostate cancer cells that are refractory to TRAIL alone as such androgen-sensitive, TRAIL-resistant cells would not be expected to have increased levels of anti-apoptotic factors such as bcl-2. Thus, Applicant respectfully requests that such secondary considerations warrant that the rejection under 35 U.S.C. § 103(a) be withdrawn.

ii. Long-Felt Need

Also, the composition of Applicant's invention provides a means to kill both androgen-sensitive and androgen-insensitive prostate cancer cells. By providing a composition utilizing low doses of TRAIL and an antiprogestin, potentially toxic effects of either compound are avoided. Prostate cancer is one of the most commonly diagnosed malignancies in men, and a leading cause of cancer-related death. Prostate cancer is a multi-focal disease with clones of androgen-sensitive and androgen-refractory cells existing in a cancer. Although androgen depletion therapy often results in regression of the tumor, a small number of androgen-dependent prostate cancer cells are often able to develop into androgen-independent cells. Also, many androgen responsive cells are very aggressive; thus, there is a compelling need for killing these cells as well as androgen insensitive cells. Thus, there is a long-felt need to be able to target both types of cells, androgen-sensitive and androgen-insensitive while the tumor is still in its early stages, so as to prevent the less invasive and less metastatic androgen sensitive cells from developing into androgen insensitive cells. Although both TRAIL and Mifepristone had been used to reduce proliferation of prostate cancer cells, Applicant's invention provides a means to more effectively kill both androgen-sensitive and androgen-insensitive prostate cancer cells, using reduced doses of TRAIL and Mifepristone, than either agent alone.

Rejoinder of Withdrawn Claims

Withdrawn process claims that depend from, or otherwise include all of, the limitations of an allowable product claim may be rejoined in accordance with the provisions of MPEP § 821.04, and such amendments will be entered as a matter of right if presented prior to allowance. Applicant has amended claims 2-12, 18-22, 25 and 26 to include the limitations of the product claims. Applicant respectfully asserts that as amended, the withdrawn claims are in a form suitable for immediate allowance, and request reentry of the amended method claims 2-12, 18-22, 25 and 26 into the application.



CONCLUSION

In view of the foregoing amendment and remarks, each of the claims remaining in the application is in condition for immediate allowance. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the outstanding rejections. The Examiner is respectfully invited to telephone the undersigned at (336) 747-7541 to discuss any questions relating to the application.

Respectfully submitted,

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Cynthia B. Rothschild (Reg. No. 47,040)

KILPATRICK STOCKTON LLP
1001 West Fourth Street
Winston-Salem, North Carolina 27101-2400
Phone: (336) 747-7541
Facsimile: (336) 607-7500